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Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive, Building 4401
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Jameson:

As a cancer epidemiologist and an invited observer at the February 1997 IARC working group evaluation of the potential human carcinogenicity of dioxin-like compounds, I have considerable interest in the resulting report and the use of that report by other organizations. It was in that context and on behalf of the American Forest and Paper Association that I submitted written comments on the *RC Draft Background Document for TCDD.* I also provided a critique of the report by Bertazzi *et al.*, entitled *Dioxin Exposure and Cancer Risk*, for consideration by members of the NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee at their 30-31 October 1997 meeting.

At that meeting, I discussed briefly my reservations about the proposal to list TCDD as a *known human carcinogen.* During his presentation of the evidence in support of that proposal, Dr. Arnold Schecter made reference to a then unpublished report by Hooiveld *et al.*, entitled *Second Follow-up of a Dutch Cohort Occupationally Exposed to Phenoxy Herbicides, Chlorophenols, and Contaminants.* Dr Schecter asserted that this unpublished paper provided additional evidence in support of the listing proposal.

The Hooiveld *et al.* report has now been published, and I have had an opportunity to review it in the context of the large body of epidemiologic literature that was examined in depth by the IARC working group during its February 1997 evaluation. On behalf of the American Forest and Paper Association, I have prepared the enclosed written comments on the Hooiveld *et al.* report for consideration by the Subcommittee in its future deliberations regarding the listing proposal for TCDD.

Thank you in advance for your assistance in bringing these comments to the attention of the Subcommittee. If I can provide any further information, please do not hesitate to contact me.

Sincerely,

Raymond S. Greenberg, MD, PhD

Comments on:
Hooiveld *et al:* Second Follow-up of a Dutch Cohort Occupationally Exposed to Phenoxy Herbicides, Chlorophenols, and Contaminants. *Am J Epidemiol* 1998;147:891-901

Raymond S. Greenberg, MD, PhD
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- **Most of the findings included in this paper were reported previously.**

This paper provides a detailed update of mortality through 1991 for a Dutch cohort of chemical manufacturing workers. A preliminary version of the current paper was published earlier (Hooiveld *et al: Organohalogen Compounds* 1996;30:185-9.) The previous publication of these data was cited in Volume 69 of the International Agency for Research on Cancer (IARC) Monograph on the Evaluation of Carcinogenic Risks to Humans, 1997. That volume provided a comprehensive review of the relationship to cancer risk of exposure to polychlorinated dibenzo-*p*-dioxins. The Dutch cohort was given focused attention in the IARC Monograph (Table 38), because it was one of four industrial populations described in the literature with presumed high levels of exposure.

In addition, the present Dutch cohort was included in the IARC multinational study of cancer risk in relation to occupational exposure to phenoxy herbicides, chlorophenols and dioxins (Kogevinas *et al: Am J Epidemiol* 1997;145:1061-75.) This multinational study also figured prominently in the IARC Monograph (Table 38.) Thus, the recent publication from the Dutch investigators adds relatively little to the already established knowledge base on the carcinogenicity of dibenzo-*p*-dioxins in general, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in particular.

- **The present findings reveal a generalized increase in mortality, rather than associations with specific outcomes.**

When assessing the likelihood that an observed exposure-disease association represents cause and effect, one of the criteria that epidemiologists typically invoke is specificity of the relationship. That is to say, an exposure is more credible as a true cause of an adverse health outcome if it does not appear to be linked indiscriminately to a wide range of outcomes. In Table 4 of the paper, 37 causes of mortality are listed, of which 26 (70%) had possibly suggestive elevations (SMR > 110) in Standardized Mortality Ratios (SMRs), including a variety of non-cancer outcomes. Only five causes of death were lower than expected based upon mortality rates in the general population. While one cannot exclude the possibility that there were true elevations in risk across this diverse set of outcomes, a more plausible explanation is that there was some systematic error (bias) which led to overestimation of the true comparative risk.

- **The present findings are inconsistent with results from other investigations of similar industrial cohorts.**

Another criterion used by epidemiologists to judge purported causal associations is the consistency of findings across studies. To the extent that findings can be independently replicated, greater credence is given to a causal interpretation. In the present context, the results reported by Hooiveld *et al.* are at odds with other key studies in several ways. For example, the excess in overall mortality was not observed in the large cohort compiled by the US National Institute for Occupational Safety and Health (NIOSH), where the SMR was 99 (Fingerhut *et al: New England Journal of Medicine* 1991;324:212-8) or with the large IARC multinational cohort (SMR = 97, Kogevinas *et al.,* 1997). There were suggestions of elevated deaths in the Dutch cohort for diseases affecting mental, nervous, and genitourinary systems, none of which were seen in the IARC multinational cohort. In the Dutch cohort, large elevations in the risk of death from cancers of the bladder and kidney were reported (SMR = 370 and 410 respectively). In contrast, these outcomes were barely above background risk in the IARC multinational cohort (SMRs = 104 and 110, respectively). Similarly, in the NIOSH cohort, the risk of renal cancer was barely above background risk (SMR = 110) and a far more modest elevation was observed in the risk of bladder cancer (SMR = 186) than was reported for the Dutch cohort (SMR = 370).

- **The ability to extrapolate the results of the serum TCDD levels from the surviving workers with measurements to the entire cohort is uncertain.**

The investigators of the Dutch cohort attempted to improve assessment of a possible dose-response relationship by collecting serum TCDD measurements on a subset of the cohort. Back-calculations then were used to impute the peak TCDD levels for these individuals and, based upon employment circumstances, the remainder of the cohort. This is a laudable goal, since many of the prior investigations of the potential adverse effects of TCDD on human health lacked any biological measurements of exposure. Unfortunately, difficulties in obtaining these serum samples, and the consequent low participation rate, limit the utility of this information.

Of the original cohort of almost 1,200 workers, a stratified sampling scheme led to the identification of 144 subjects for serum measurements. Of these individuals, only 47 (33%) actually had useable serum results. The extent to which these individuals validly characterize the original cohort is uncertain and a variety of selection factors may be operating. Those who did participate may have had unusually high exposures, or conversely, may represent the "worried well." In the absence of samples more proximate to the time of exposure and on a larger proportion of the eligible cohort, inferences based upon the serum measurements obtained must be viewed as speculative.

- **In general, the risk of adverse health outcomes does not appear to rise in a smooth graded fashion with increasing imputed maximum levels of TCDD exposure.**

An additional important criterion in judging the likelihood of a causal interpretation is the extent to which the risk of an adverse health outcome rises with increasing level of exposure. The results of the present analysis, (as shown in Table 7 of the current publication), do not show the kind of rising risk from low to medium to high levels of exposure that one would typically associate with causation. For example, the relative risk of all causes of death rises to 1.9 at the medium TCDD level without any further increase at the highest level of exposure. The relative risk for all cancer deaths combined rises to 4.8 at the medium level of exposure, remaining essentially constant for the highest exposure group. The same pattern is seen for cancers of the lung and respiratory system. For malignancies of the urinary organs, the risk rises in the mid-exposure group, only to fall back to the baseline level for the highest exposure category. The elevation in risk for non-Hodgkin's lymphoma essentially was confined to the highest exposure group.

The strongest evidence of a graded increase in risk across exposure levels was seen for accidents, poisoning and violence, with a relative risk rising to 2.2 in the medium exposure group and 5.9 in the highest exposure group. The subset of these events that were classified as suicides also demonstrated an apparent gradient of effect, but this was based on small numbers (two observed deaths each among exposed and non-exposed persons). There is no obvious biological explanation for imputing a cause-and-effect relationship between TCDD exposure and these accidental and violent causes of death.

Although one cannot exclude the possibility of a saturation effect for TCDD exposure by which risk rises at moderate exposure and then levels off or declines, this is not the pattern of risk elevation seen with virtually all known carcinogens. Other epidemiologic studies that have examined TCDD dose (imputed from serum measurements) and risk of cancer deaths have not found the shape of relationship reported by Hooiveld and coworkers. For example, Flesch-Janys *et al.*, (*Am J Epidemiol* 1996;144:716) reported essentially no increase in risk of cancer death up until the highest decile of imputed exposure level. Even at the highest exposure level, the relative risk was half as large as the elevation reported for mid-level exposure by Hooiveld *et al.* Ott and Zober (*Occup Environ Med* 1996;53:606-12) reported a smooth gradient of elevation in risk of death from cancer across four levels of imputed TCDD level of exposure. Again, the highest elevation of relative risk observed by Ott and Zober was less than half that reported by Hooiveld and colleagues in their mid-level of exposure category.

The inconsistency of the Hooiveld *et al.* dose-response data with all other extant epidemiology raises questions about whether the observed risk elevation arose

from some systematic error. That is to say, there may be something about the workers in the exposed groups other than exposure to TCDD *per se* that resulted in their apparent increase in risk for adverse health events. These other risk factors, also known as confounders, might include other industrial exposures encountered by these workers, as well as other non-occupational lifestyle characteristics. The fact that such other exposures might explain the observed relationships was demonstrated in a case-control study nested within the IARC multinational cohort (Kogevinas *et al: Epidemiology* 1995;6:396-402). In that study, the investigators found a graded dose-response relationship between level of TCDD exposure and risk of non-Hodgkin's lymphoma, but they also found an equally strong graded relationship with estimated level of exposure to 2,4,5-trichlorophenoxyacetic acid. In the absence of concurrent data on estimated levels of exposure to other risk factors, one cannot definitively exclude confounding as a possible explanation for the findings of Hooiveld and coworkers.

Conclusion

The findings reported in the present publication have been presented elsewhere in the peer-reviewed literature and were already included in the IARC assessment of the carcinogenicity of TCDD. Although a number of statistical associations between TCDD exposure and adverse effects on human health are reported, the pattern of these findings is not consistent with a causal interpretation. The conventional epidemiologic criteria for causation that are **not** satisfied by these results are: (1) demonstration of a graded dose-response relationship; (2) consistency with findings from other studies; and (3) specificity of association with particular outcomes.

In conclusion, the present findings add no substantive new evidence regarding possible adverse effects on human health from exposure to TCDD.